AF Burden and Anticoagulation: When Have We Crossed the Threshold?

Craig S. Cameron, MD, FACC, FHRS

Oklahoma Heart Institute

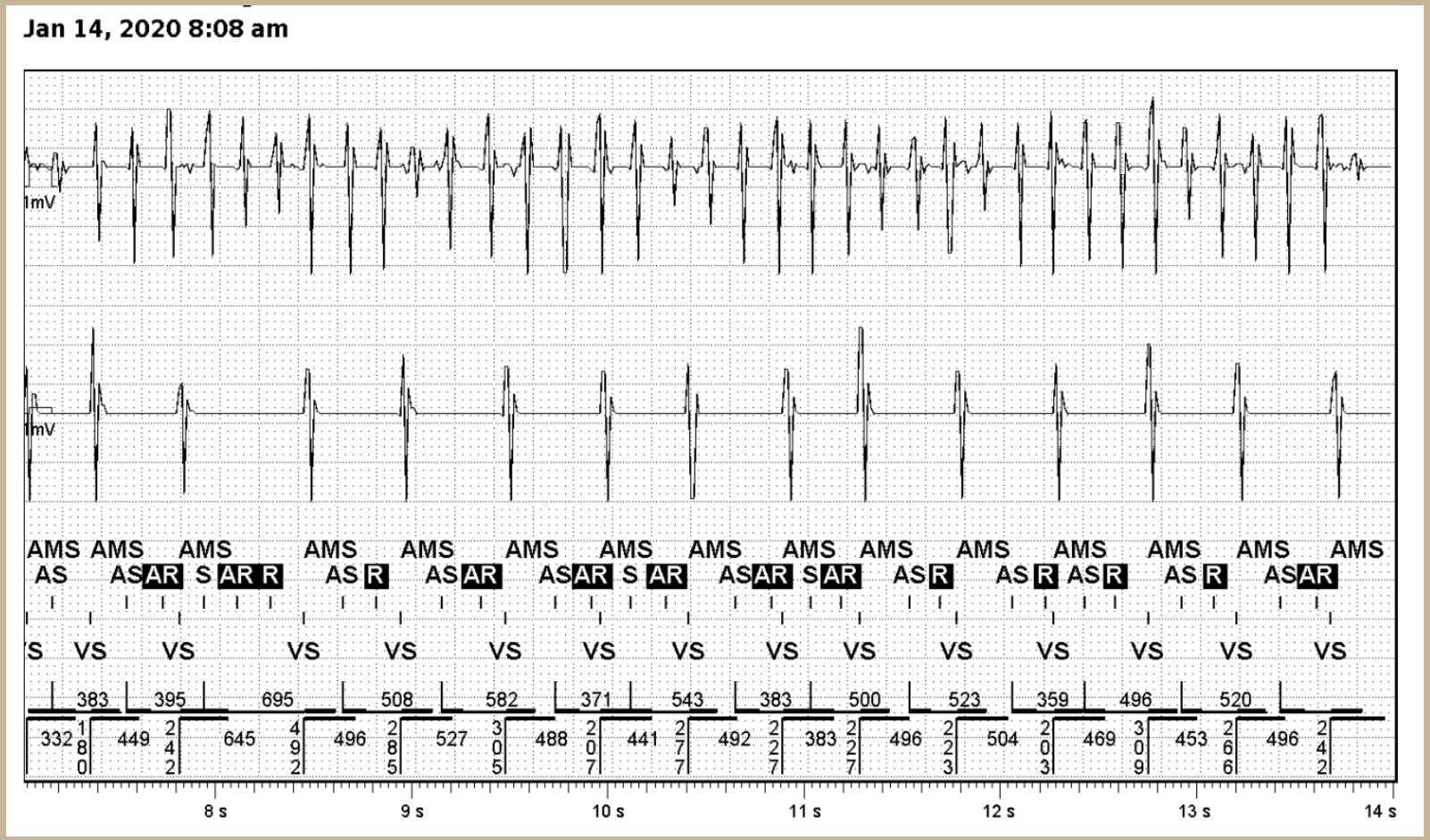
No Relevent Disclosures

Happy Valentine's Day!

63 yo man with hypertension, sinus node dysfunction and episodes of asymptomatic AF recorded by PPM:

Episodes

Date / Time	Type	Peak A / V Rate (bpm)	Duration (D:H:M:S)
Jan 14, 2020 5:59 am	AMS Entry	640 / 167	0:02:08:42
Jan 14, 2020 12:28 am	AMS Entry	640 / 137	0:05:31:02
Jan 12, 2020 7:35 am	AMS Entry	199 / 61	0:00:00:06
Jan 4, 2020 11:52 am	AMS Entry	301 / 122	0:00:01:10
Jan 4, 2020 11:51 am	AMS Entry	295 / 110	0:00:00:18
Jan 4, 2020 11:47 am	AMS Entry	301 / 124	0:00:03:48
Jan 4, 2020 11:45 am	AMS Entry	290 / 123	0:00:01:28
Jan 4, 2020 11:45 am	AMS Entry	341 / 121	0:00:00:10
Jan 4, 2020 11:44 am	AMS Entry	233 / 85	0:00:00:06
Jan 4, 2020 11:44 am	AMS Entry	265 / 122	0:00:00:14
Jan 4, 2020 11:44 am	AMS Entry	199 / 74	0:00:00:04
Jan 4, 2020 11:43 am	AMS Entry	279 / 121	0:00:00:52
Jan 4, 2020 11:35 am	AMS Entry	313 / 122	0:00:01:52
Jan 4, 2020 11:34 am	AMS Entry	279 / 122	0:00:01:40



Would you anticoagulate?

A. Yes

B. No

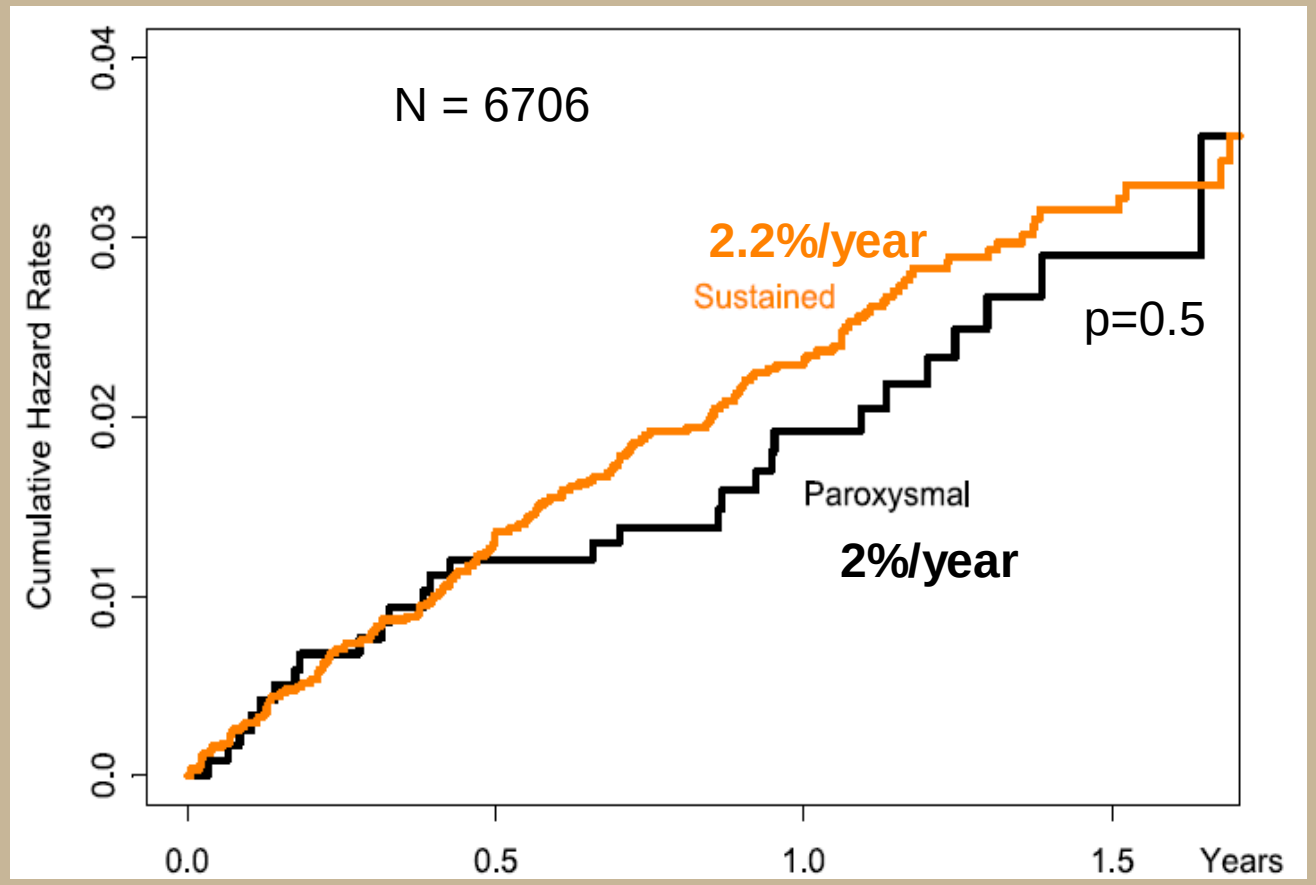
2019 AF Guidelines and Anticoagulation

Class of Recommendation	Level of Evidence	Anticoagulation Recommended For:
I	A, B	Patients with NVAF and an elevated CHA2DS2-VASc score of 2 or greater in men or 3 or greater in women, oral anticoagulants are recommended. Options include: • Warfarin (LOE: A) (S4.1.1-5–S4.1.1-7) • Dabigatran (LOE: B) (S4.1.1-8) • Rivaroxaban (LOE: B) (S4.1.1-9) • Apixaban (LOE: B) (S4.1.1-10), or • Edoxaban (LOE: B-R) (S4.1.1-11)
IIb	C	Patients with NVAF and a CHA2DS2-VASc score of 1 in men and 2 in women, prescribing an oral anticoagulant to reduce thromboembolic stroke risk may be considered (S4.1.1-31–S4.1.1-35).

January CT, et al. 2019 Focused Update on Atrial Fibrillat

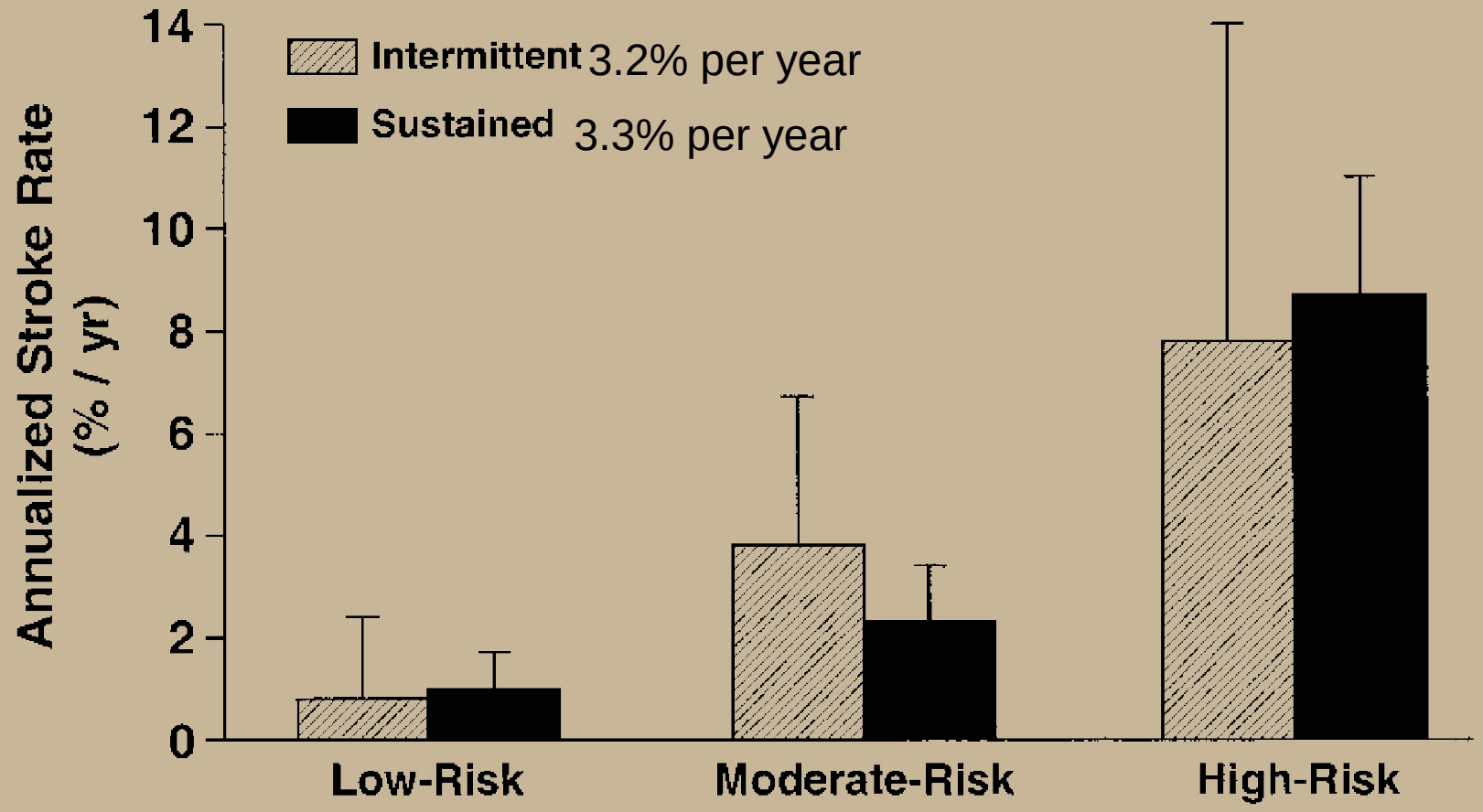
Risk of Stroke

Paroxysmal versus Sustained



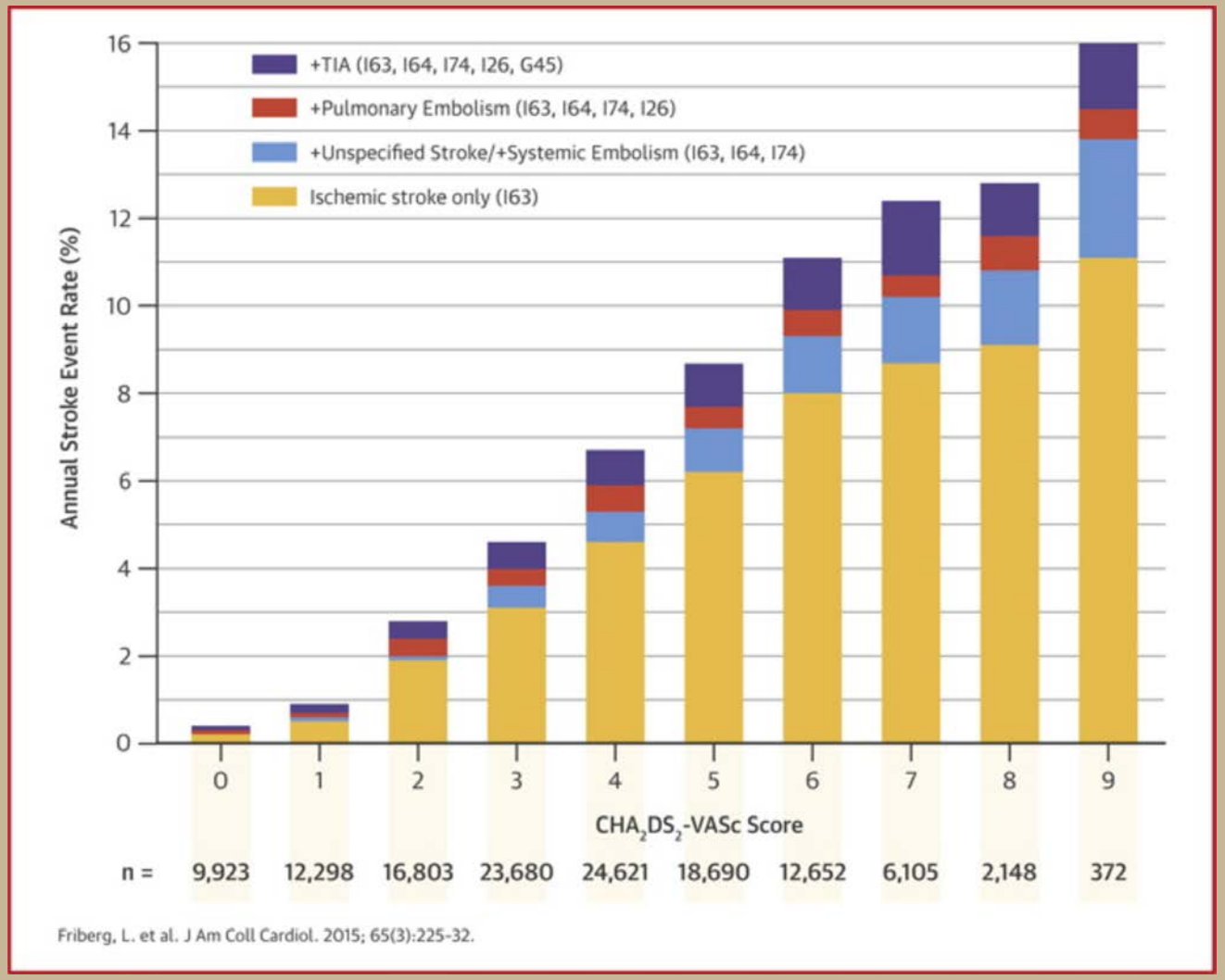
Hohnloser SH et al. *J Am Coll Cardiol* 2007; 50:2156

SPAF Studies
Ischemic Stroke Risk



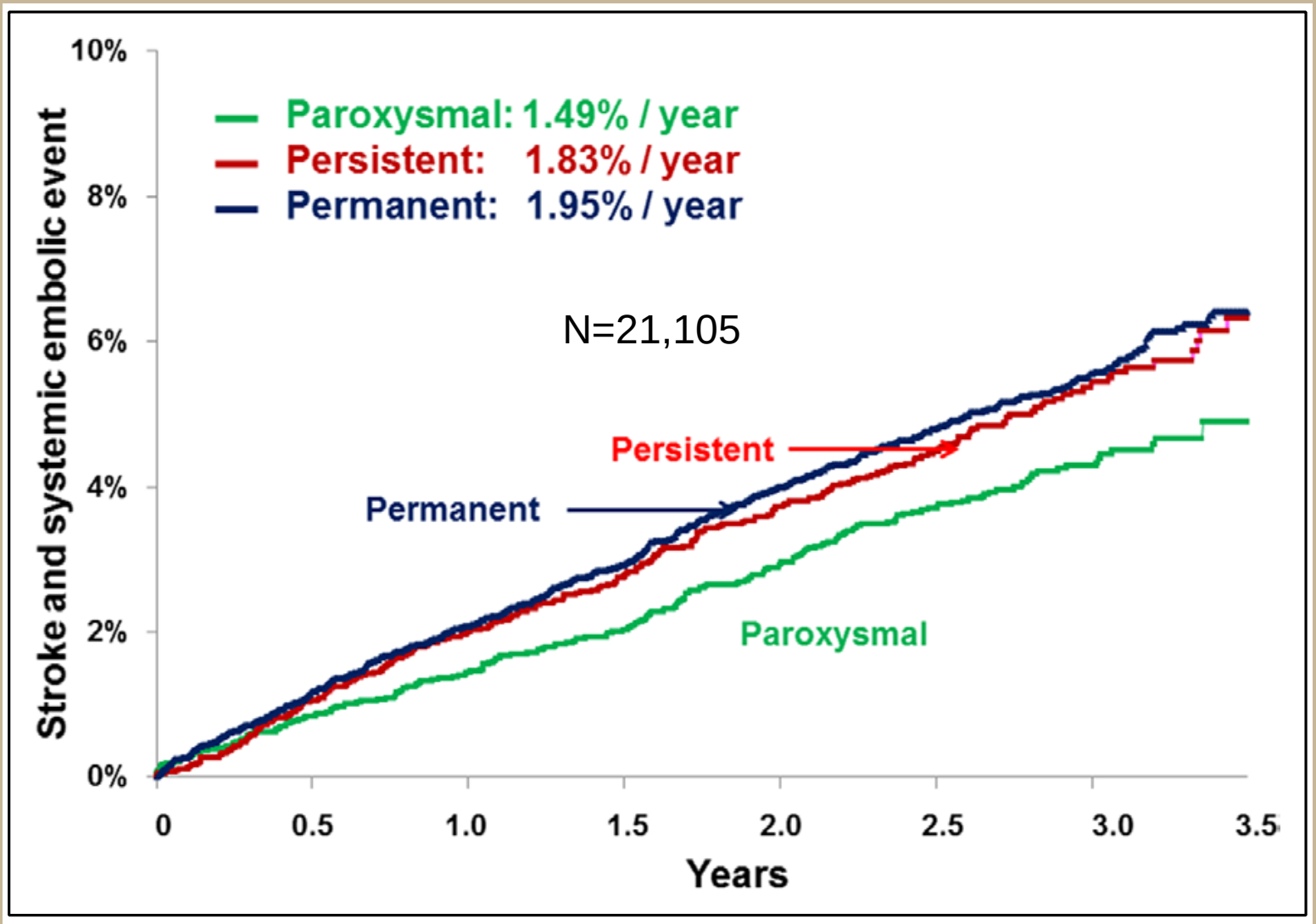
J Am Coll Cardiol 2000;35:183–7

CHA_2DS_2VASc Predicts Events



J Am Coll Cardiol. 2015;65(3):225-232.

ENGAGE AF-TIMI 48



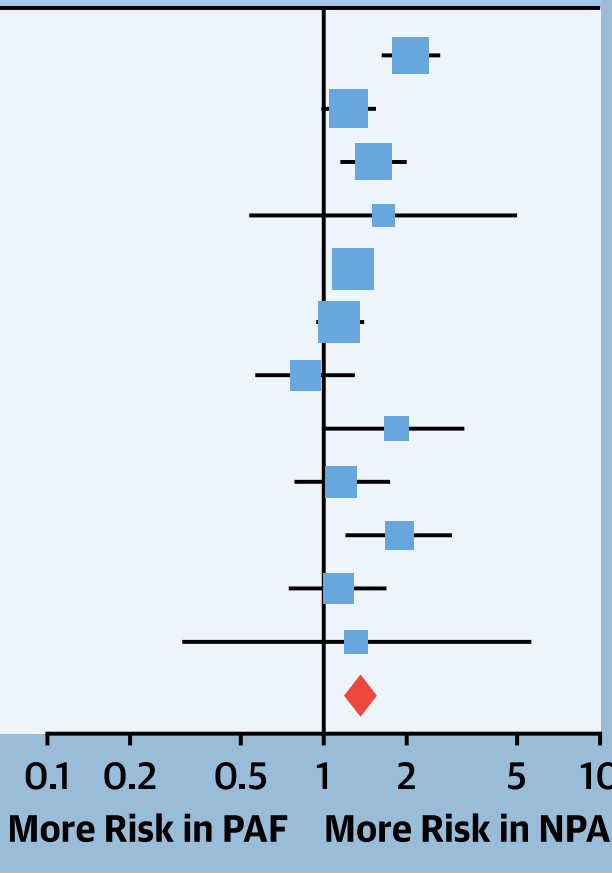
Circ Arrhythm Electrophysiol. 2017;10:e004267. DOI:10.1161/CIRCEP.116.004267

Replicated in post-hoc analyses of:

- ARISTOTLE
- ROCKET-AF
- ACTIVE A
- AVERROES

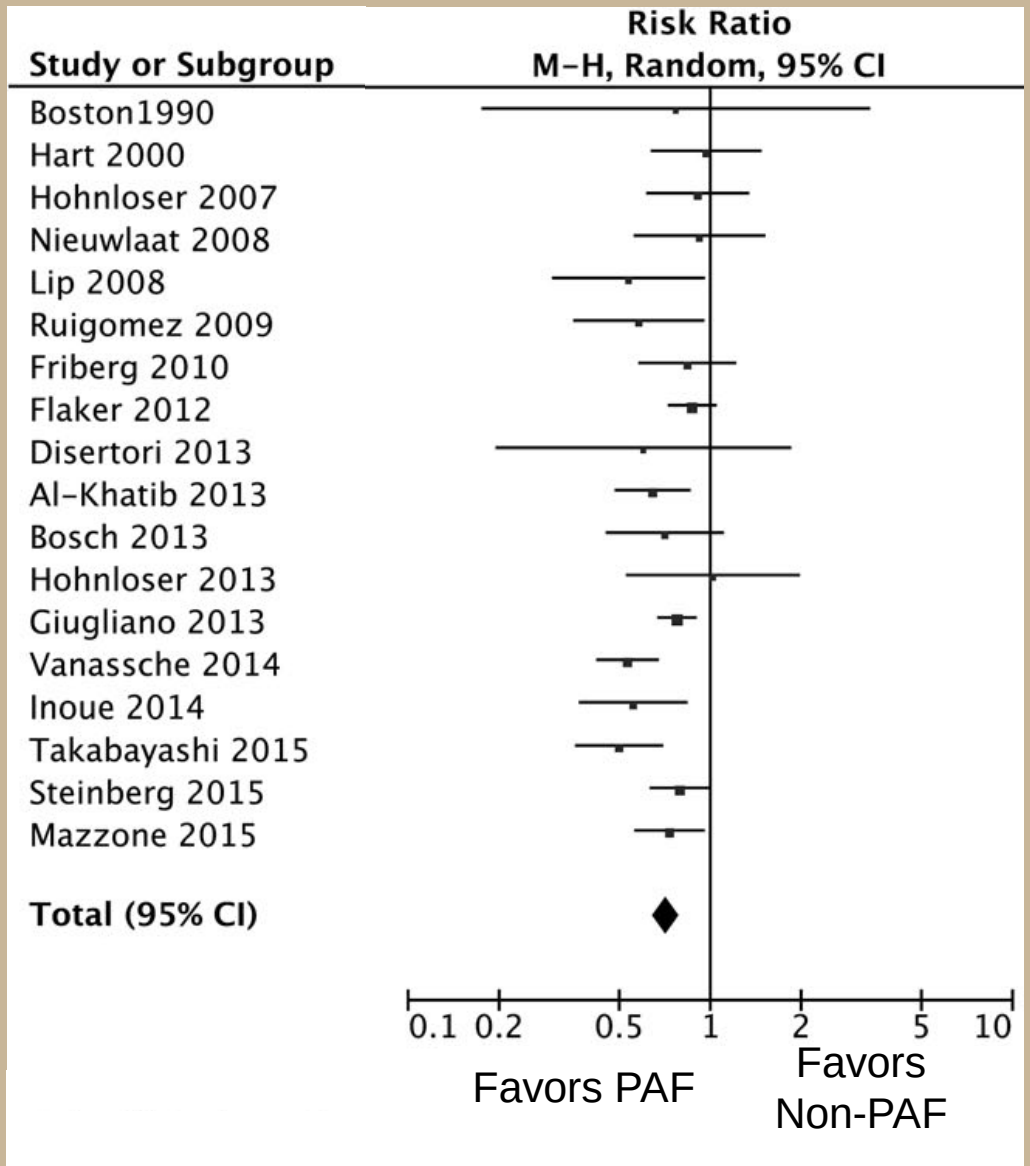
Stroke or Systemic Embolism

Study name	Risk Ratio	Lower Limit	Upper Limit	p-Value
AVERROES and Active A	2.071	1.631	2.630	0.000
ROCKET-AF	1.229	0.980	1.542	0.074
ARISTOTLE	1.510	1.133	2.013	0.005
GISSI-AF	1.665	0.540	5.133	0.375
ENGAGE AF	1.290	1.094	1.520	0.002
RE-LY	1.148	0.955	1.381	0.141
Euro Heart Survey	0.855	0.566	1.291	0.455
SPORTIF	1.845	1.033	3.299	0.039
Active W	1.169	0.790	1.730	0.434
ELAT	1.878	1.193	2.954	0.006
SPAF	1.131	0.750	1.705	0.558
BAATAF	1.300	0.300	5.634	0.726
OVERALL	1.355	1.169	1.571	0.000



Eur Heart J 2016;37:1591–602.

Stroke or Systemic Embolism: Meta-Analysis II

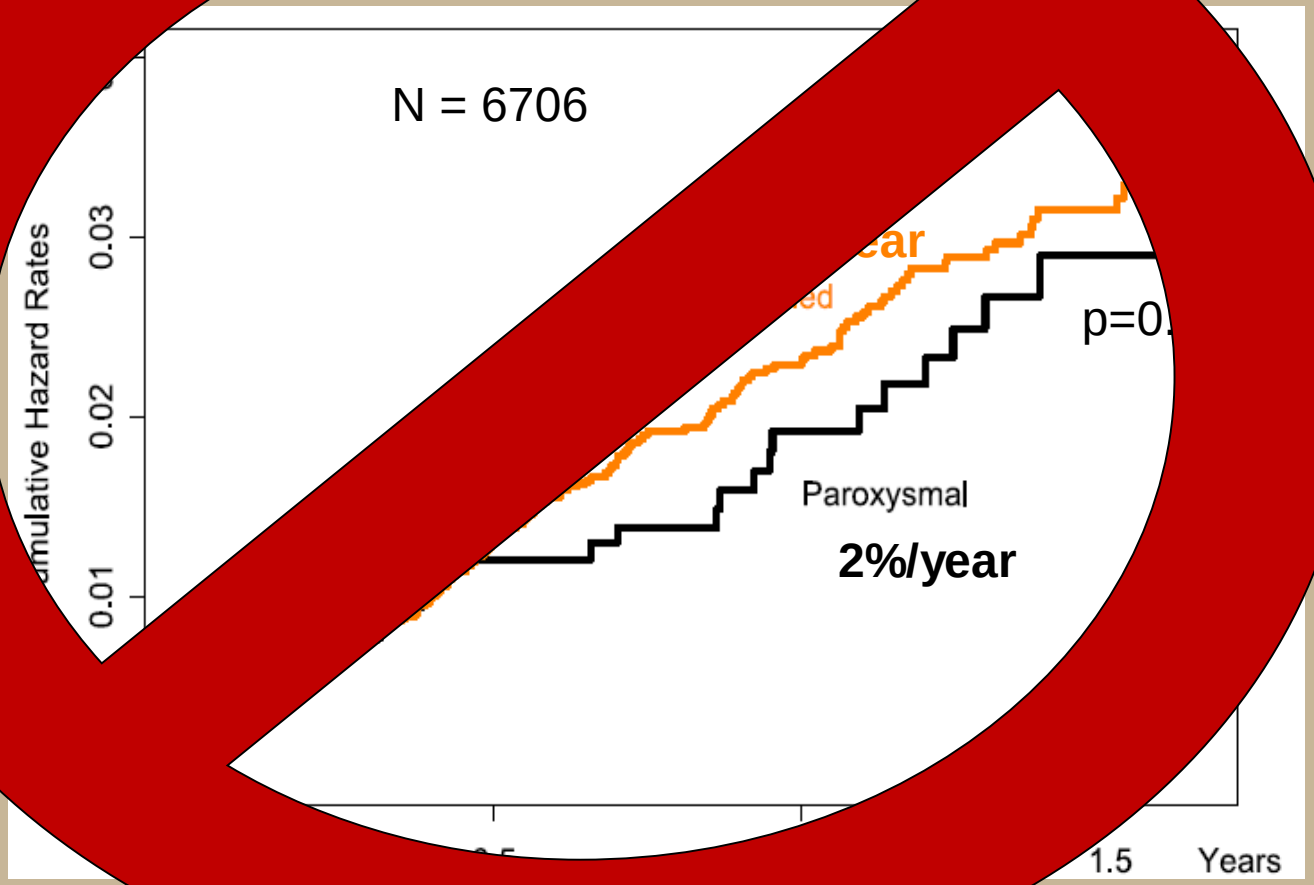


- 18 studies
- 239,528 patient-years
- Stroke or SE incidence:
  - 1.6% in paroxysmal
  - 2.3% nonparoxysmal
- RR: 0.72
  - 95% CI: 0.65 to 0.80
  - $p < 0.001$

Clin Cardiol 2017;40:641–7.

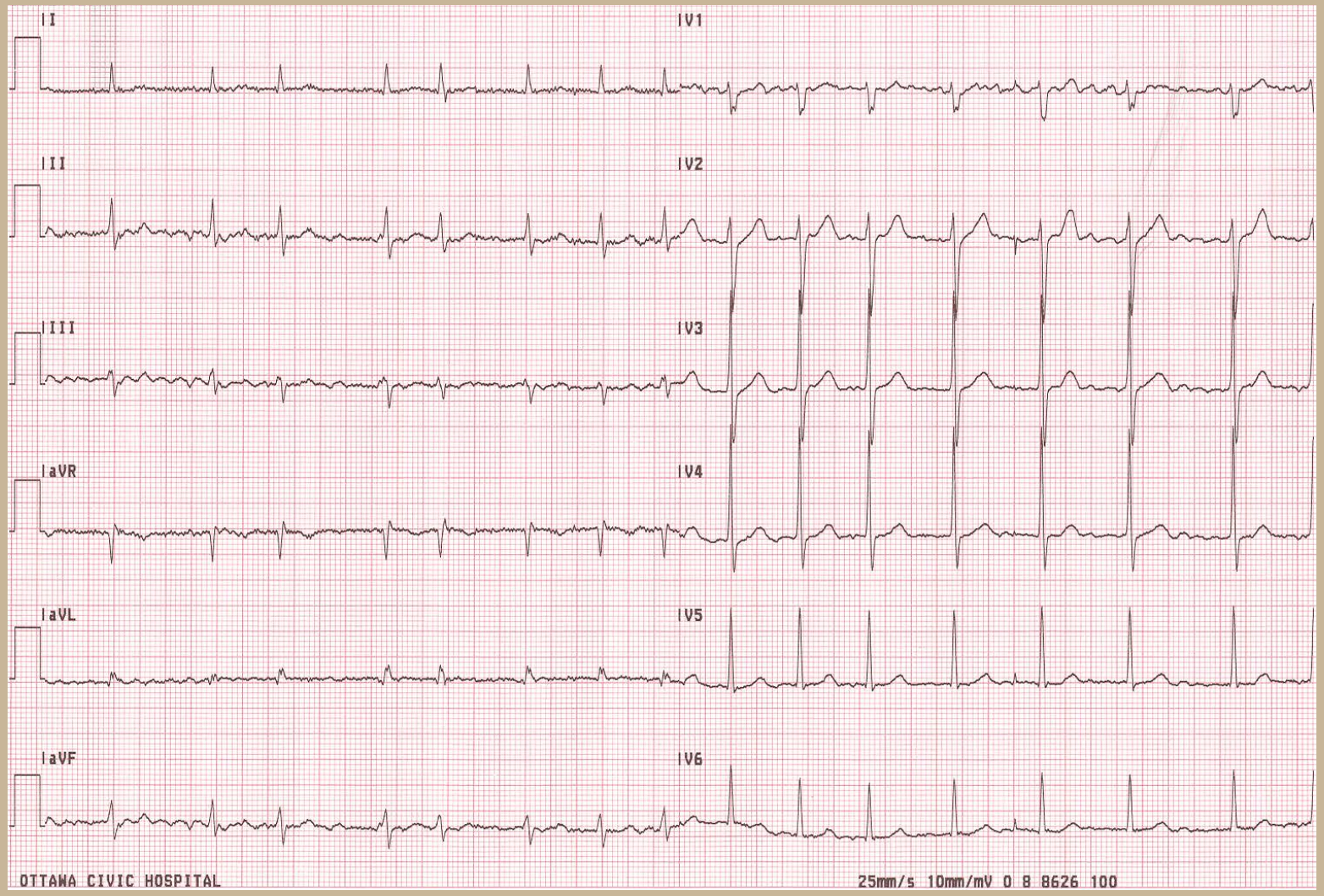
ke

ysmal versus ed



Hohnloser … *Cardiol* 2007; 50:2156

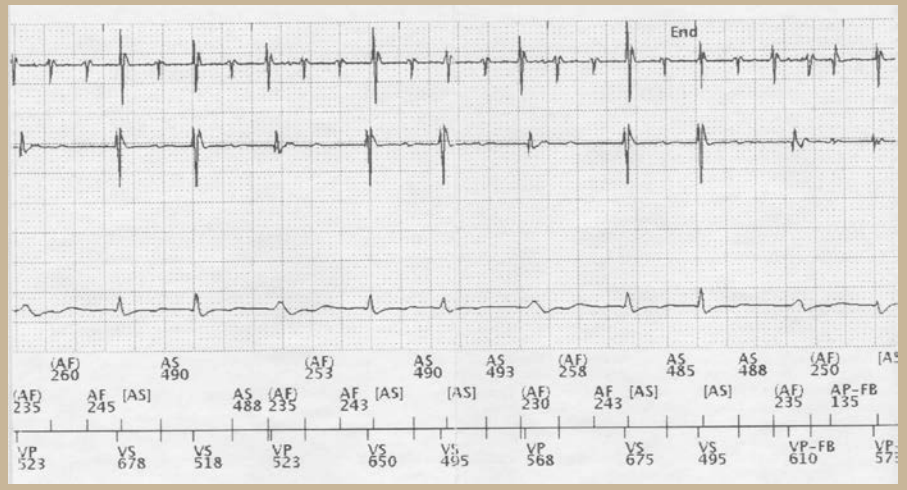
What is Atrial Fibrillation?



AF Terminology

- Silent AF
- Sub-clinical AF (SCAF)
- Device Detected AF
- CIED Detected AF
- AHREs

SCAF Detected by Cardiac Devices



- Would not be detected by means other than a device with continuous (24/7) long-term recording
- Is usually asymptomatic
- Episodes are usually short in duration (minutes to hours)
- The specificity of CIED-detected AHREs differs
  - Between individual devices
  - Improves as episode duration exceeds several hours
  - Specificity even lower with ILRs which do not have an atrial lead

What percentage of CIED patients have subclinical AF?

A. 10%

B. 20%

C. 30%

D. 50%

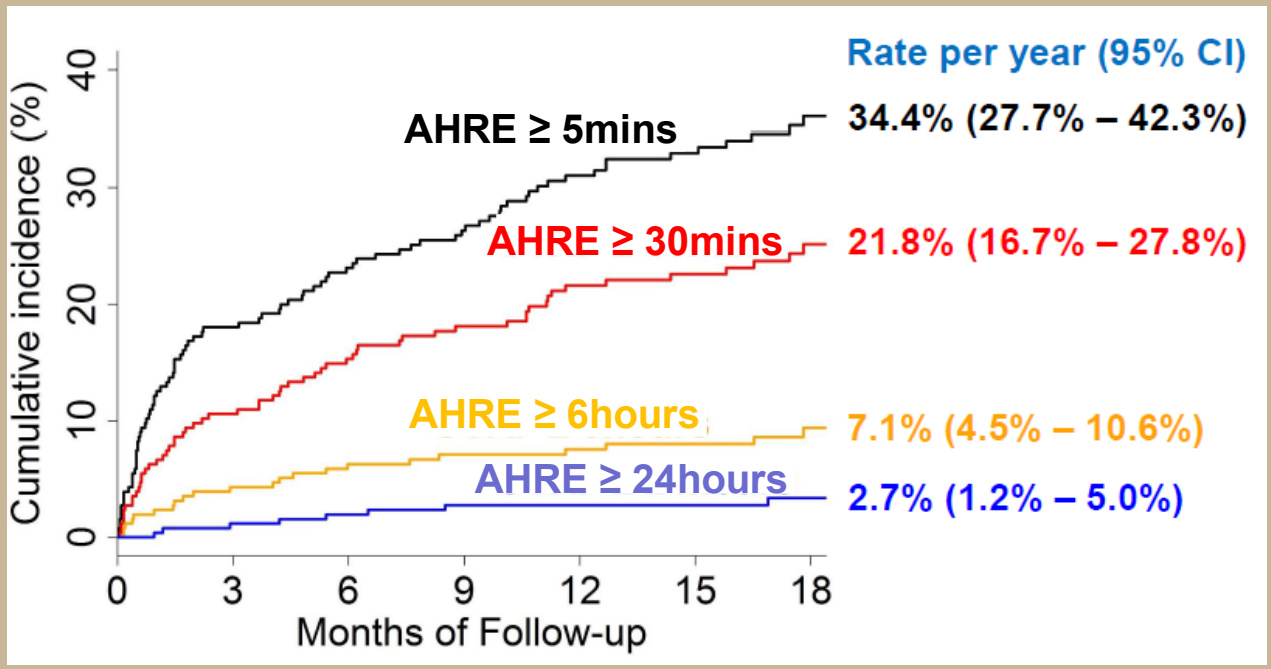
E. 70%

Incidence of AF Detected in the Implanted Device Population

Year	Trial	Device Indication	Clinical Profile of Patients	Incidence of Newly Detected AF
2002	Gillis et al.[46]	PPMs for sinus node disease	All	157/231 (68%)
2003	MOST[47]	PPMs for sinus node disease	All	156/312 (50%)
2010	TRENDS[33]	PPMs and ICDs All indications	History of prior stroke No history of AF No OAC use ≥1 stroke risk factor	45/163 (28%)
2012	TRENDS[32]	PPMs and ICDs All indications	No history of prior stroke No history of AF No OAC use ≥1 stroke risk factor	416/1368 (30%)
2012	ASSERT[31]	PPMs and ICDs All indications	History of hypertension No history of AF No OAC use	895/2580 (34.7%)
2013	Healey et al.[48]	PPMs All indications	All	246/445 (55.3%)

ASSERT II: AHRE episodes are common

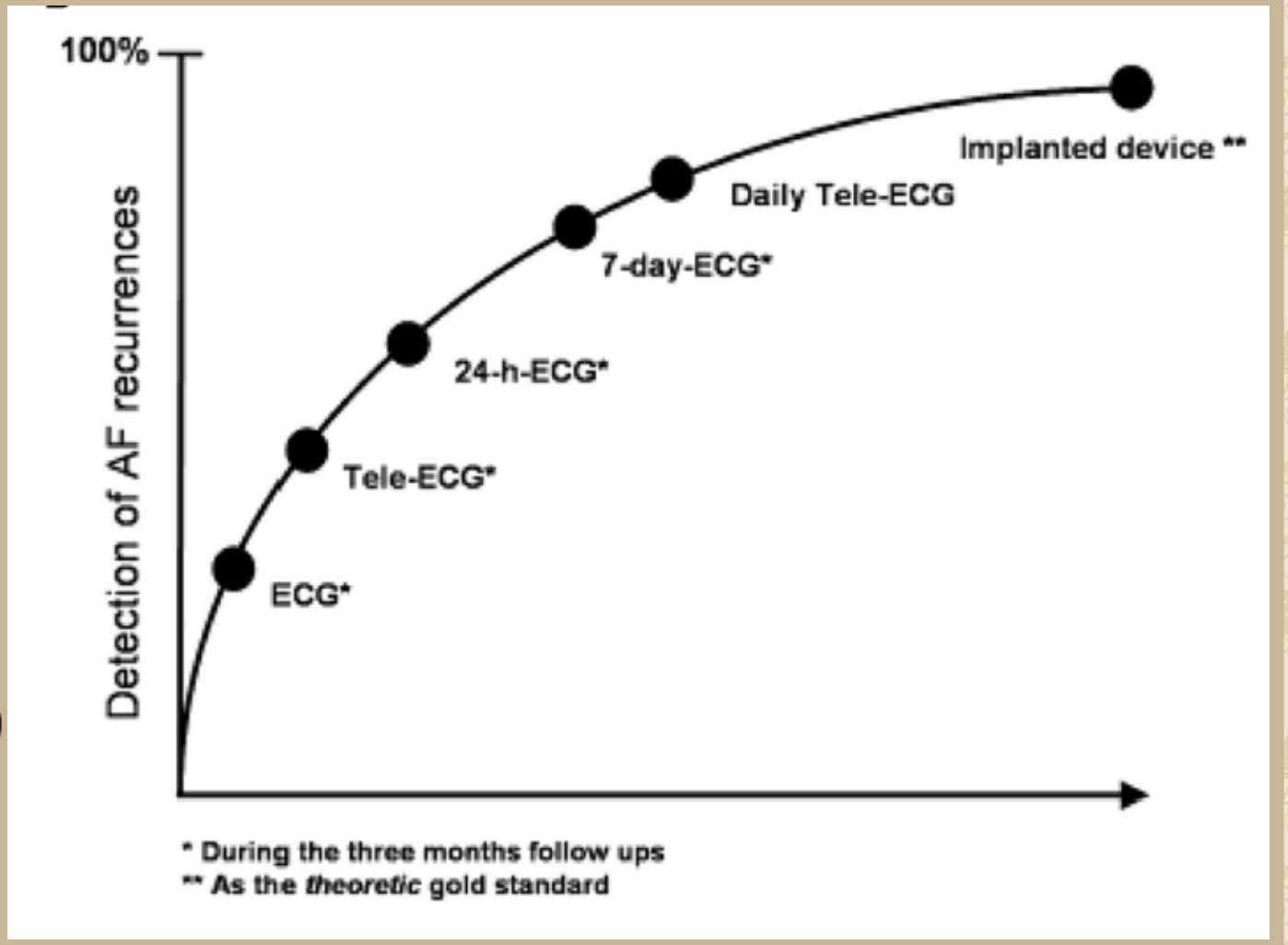
ASSERT II: ILR implantation in 256 patients enrolled for research purposes (mean age 74 years, mean CHADSVASC score 4.1)



Healey JS et al. Circulation.(2017)

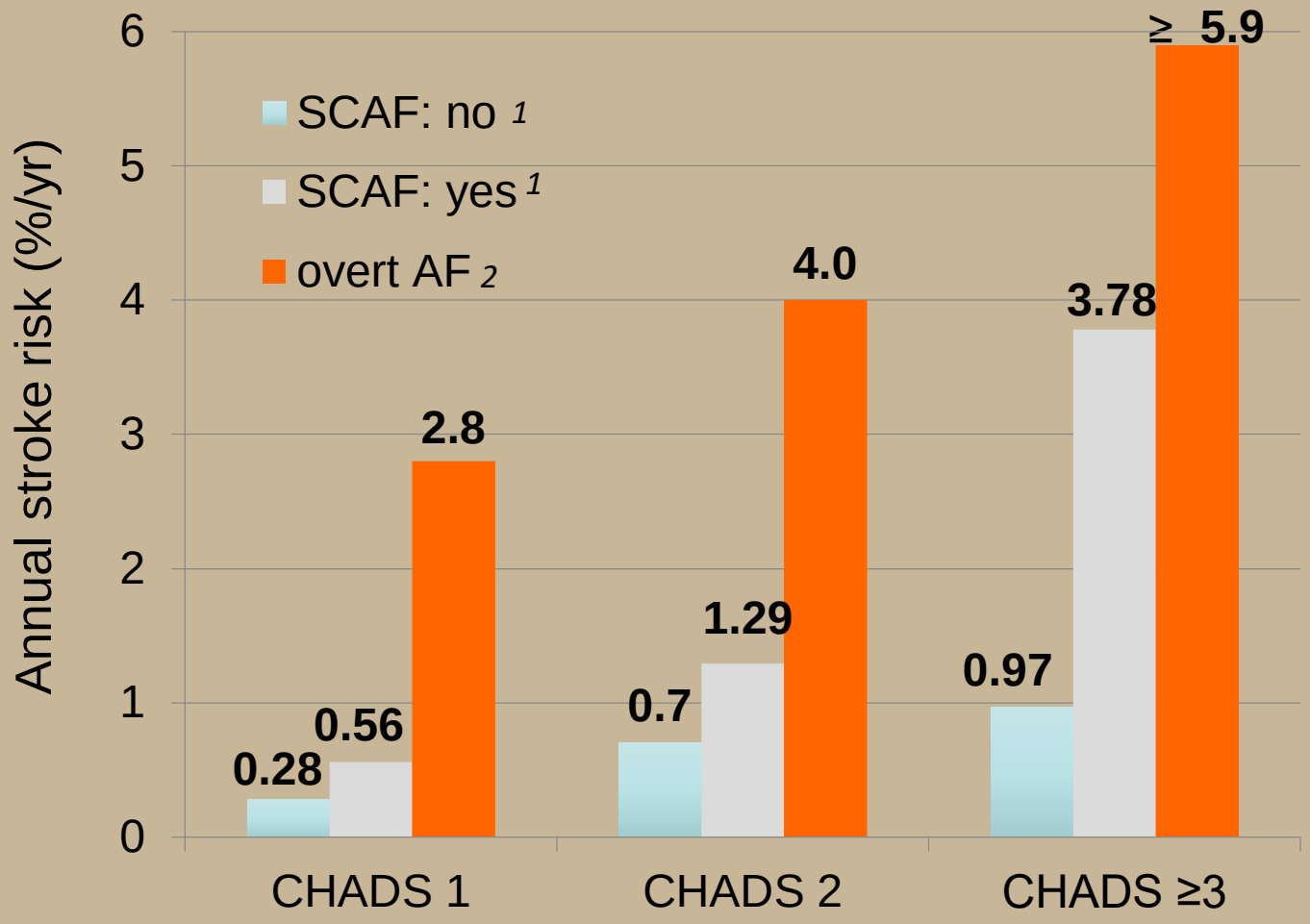
Prevalence of AF in Patients with Stroke Risk Factors

Year	Study	Number of Patients	Clinical Profile	Duration of F/u	Incidence of AF
2016	ASSERT II	256	Age > 65 Mean CHADSVASC 4	18 mos	AF > 5 mins 34% AF > 30 mins 22% AF > 6 hours 7% AF > 24 hours 2.7%
2017	Reveal AF	385	Mean CHADS 2.9 Mean CHADSVASC 4.4	18 mos	AF > 6 mins 29.3%
2017	Predate AF	245	CHA2DS2-VASc score ≥ 2	15 mos	AF > 6 mins 22%



Arya et al. *PacingClin.Electrophysiol. 30, 458-462 2007*

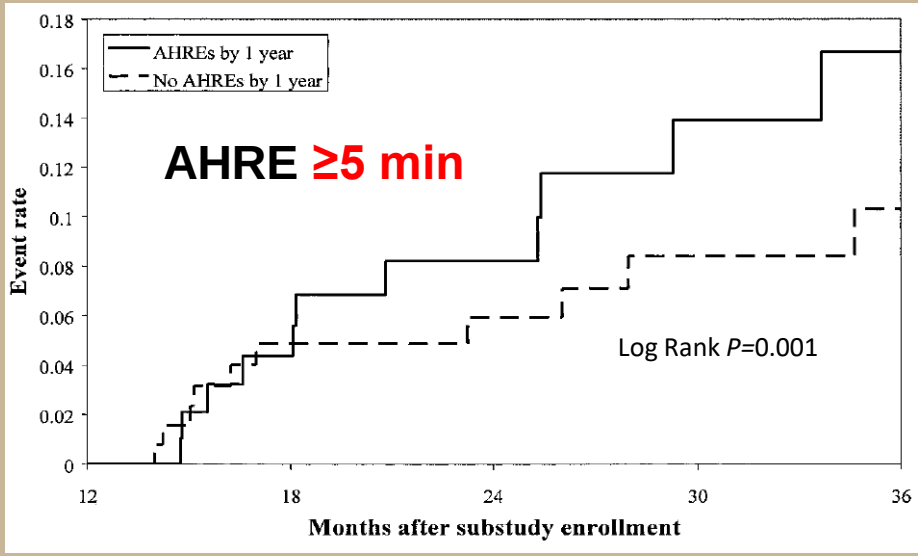
Stroke Risk for SCAF is Lower than AF

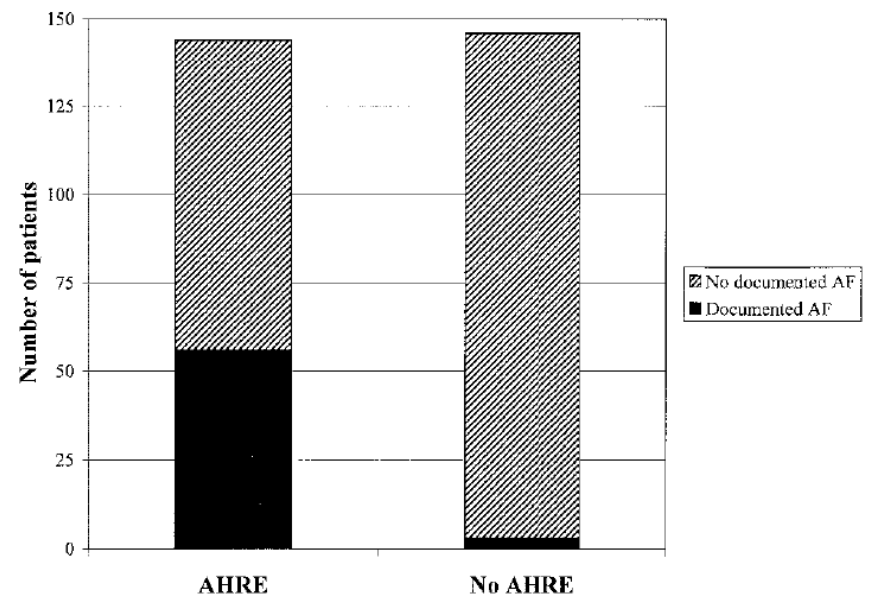


[1]*Healey JS et al. N Engl J Med. 2012;366:120–9*
[2]*Gage BF et al. JAMA. 2001;285:2864–70*

MOde Selection Trial (MOST)-subgroup

312 patients





- Total mortality (HR 2.48 [1.25, 4.91], *P*=0.0092)
- Death/nonfatal stroke (HR 2.79 [1.51, 5.15], *P*=0.0011)

- AF (HR 5.93, *P*=0.0001)

Glotzer TV et al. Circulation. 2003;107:1614-19.

The clinical significance of atrial arrhythmias detected by implanted device diagnostics (TRENDS)

- 2,486 patients (≥1 stroke risk- CHADS2)
- AT/AF burden subsets in preceding 30 day window: zero, low (<5.5 h) and high (≥ 5.5 h)

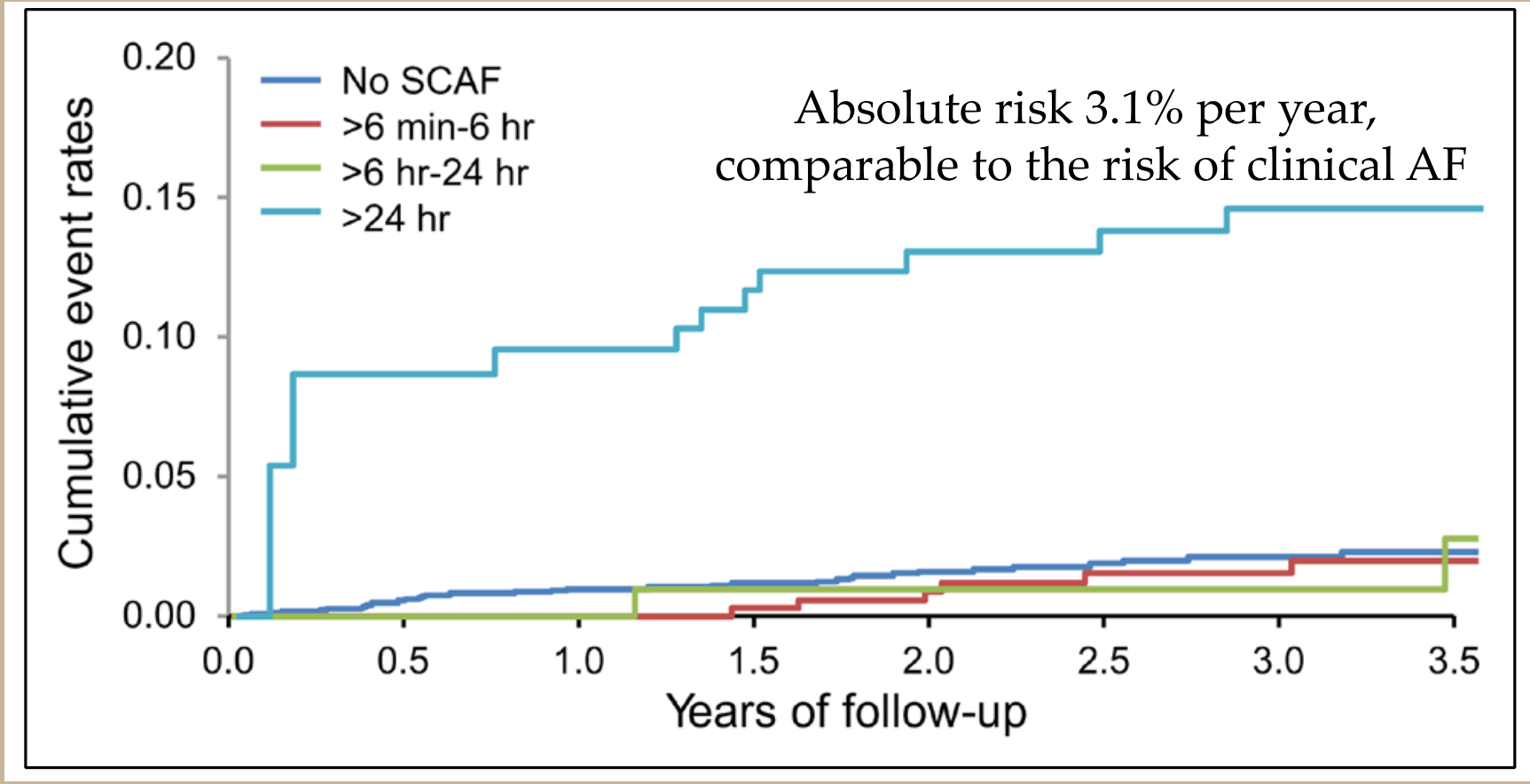
Table 2. TE Rates for the Overall Study Group (Unadjusted)

AT/AF Burden Subset	Annualized TE Rate (95% CI), %	Annualized TE Rate Excluding TIAs (95% CI), %
Zero AT/AF burden	1.1 (0.8–1.6)	0.5 (0.3–0.9)
Low AT/AF burden (<5.5 h)	1.1 (0.4–2.8)	1.1 (0.4–2.8)
High AT/AF burden (5.5 h)	2.4 (1.2–4.5)	1.8 (0.9–3.8)

Glotzer TV et al. Circ Arrhythmia. Electrophysiol. 2009;2:474-480.

ASSERT – Post Hoc

2580 patients receiving a pacemaker or ICD, aged >65 years with hypertension, without prior AF



Eur Heart J. 2017;38:1339–134

Study	Size	Follow up median	Prior AT/AF (%)	Mean CHADS2	AHRE min rate (bpm)	AHRE minimum duration	AHRE rate (%)	SCAF threshold for TE risk	Annual TE rate (%)	TE HR
MOST$_{sub}$ Glotzer et al. 2003	312	2.3 yr	60	-	>220, 10 beats	>5 min	51.3	>5 min	2.2	2.8*
Italian AT500 Capucci et al. 2005	725	1.8 yr	100	-	PR Logic	≥5 min	78.9	>24 h	1.2	3.1
TRENDS Glotzer et al. 2009	2,486	1.4 yr	20	2	>175, ≥20 s	window burden	24.0	>5.5 h ≥10.8 h/30 d	2.4 -	2.2¥ 2.2¥
ASSERT Healy et al. 2012	2,850	2.5 yr	0	~ 2	>190	>6 min	34.7	>6 min	1.8	2.5
Home Care and everesT Shanmugam et al. 2012	560	370 d	32	2	>180	14 min/d or 1%/d	40.0	3.8 h	4.9 (8.7%¶)	9.4
IMPACT Martin et al. 2015	2,718	2 yr	12	-	≥200	≥36/48 beats	34.8	Any AHRE	1.5	-
RATE Registry Swiryn et al, 2016	5,379	1.9 yr	0	2	-	≥3 cons. PACs	¶¶	Long episodes	¶¶	

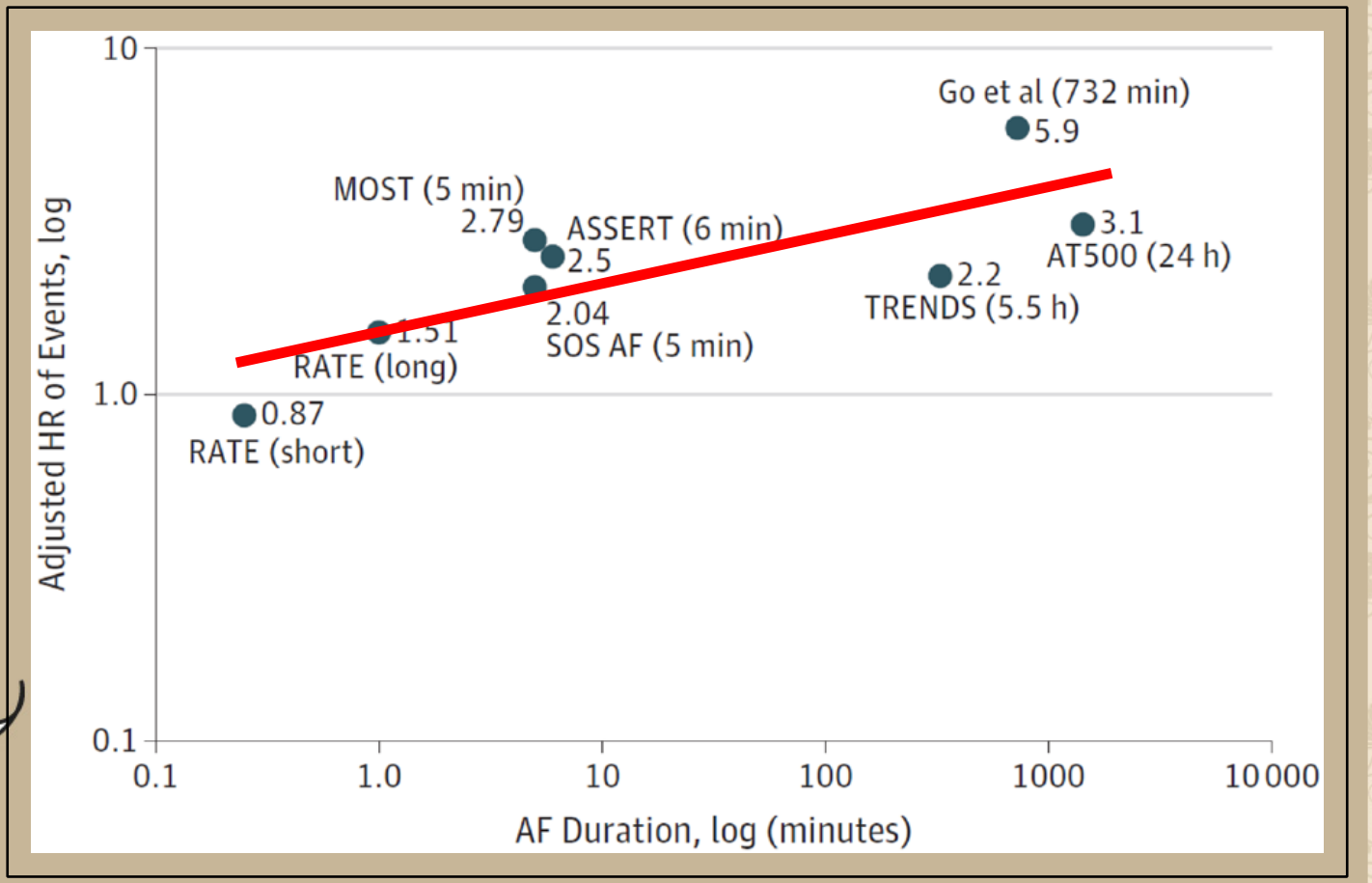
*Death or stroke

¶P=0.06

¥excluding patients with prior AF history

¶¶Rates were adjudicated

AF Burden and TE Risk

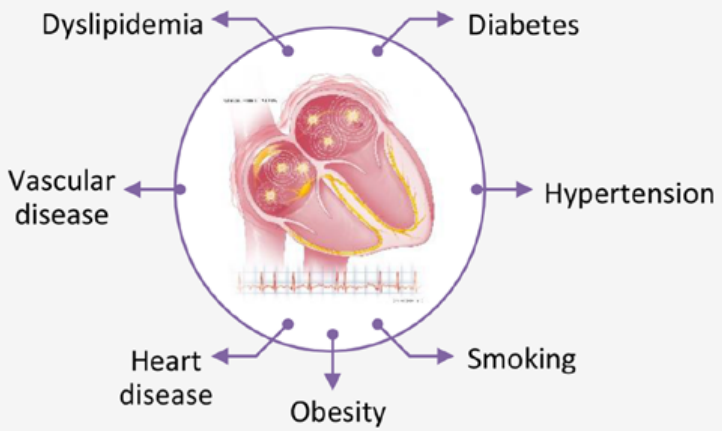
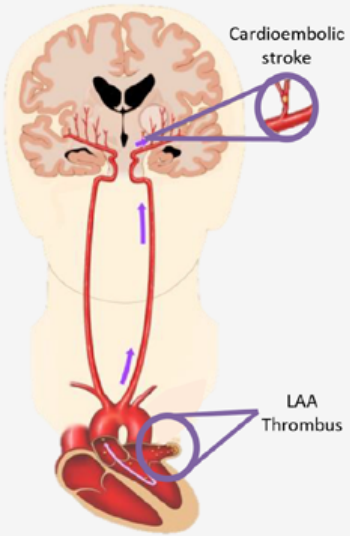


Circulation. 2019;140:e944–e963

Temporal Relationship of Device-Detected AF to Thromboembolic Events

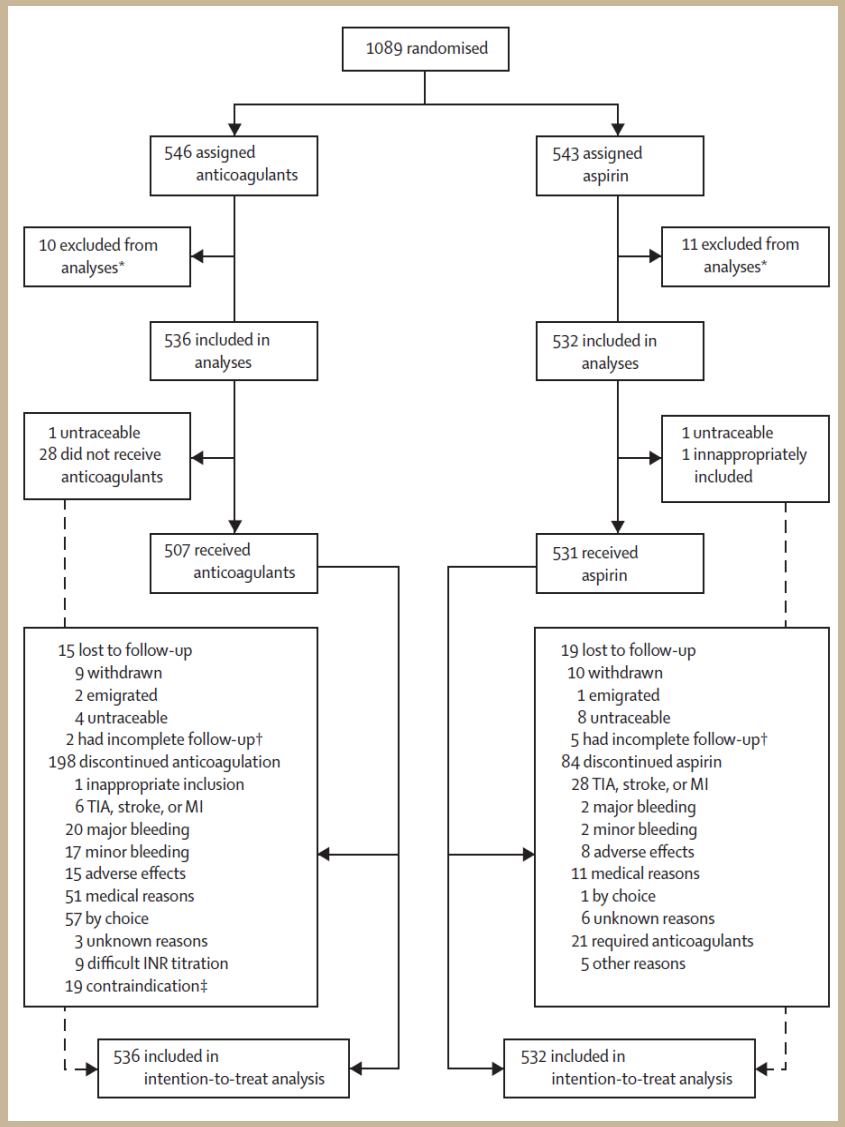
Year	Trial	Number of pts with TE Event	Definition of AF episode	Any AF Detected prior to TE event	AF Detected only AFTER TE event	NO AF in 30 days Prior to TE event	Any AF in 30 days Prior to TE event
2011	TRENDS	40	5 mins	20/40 (50%)	6/40 (15%)	29/40 (73%)	11/40 (27%)
2014	ASSERT	51	6 mins	18/51 (35%)	8/51 (16%)	47/51 (92%)	4/51 (8%)
2014	IMPACT	69	36/48 atrial beats > 200 bpm	20/69 (29%)	9/69 (13%)	65/69 (94%)	4/69 (6%)
2015	Turkaharia et al.	187	5.5 hours	36/187 (19%)	NA	NA	15/187 (8%)

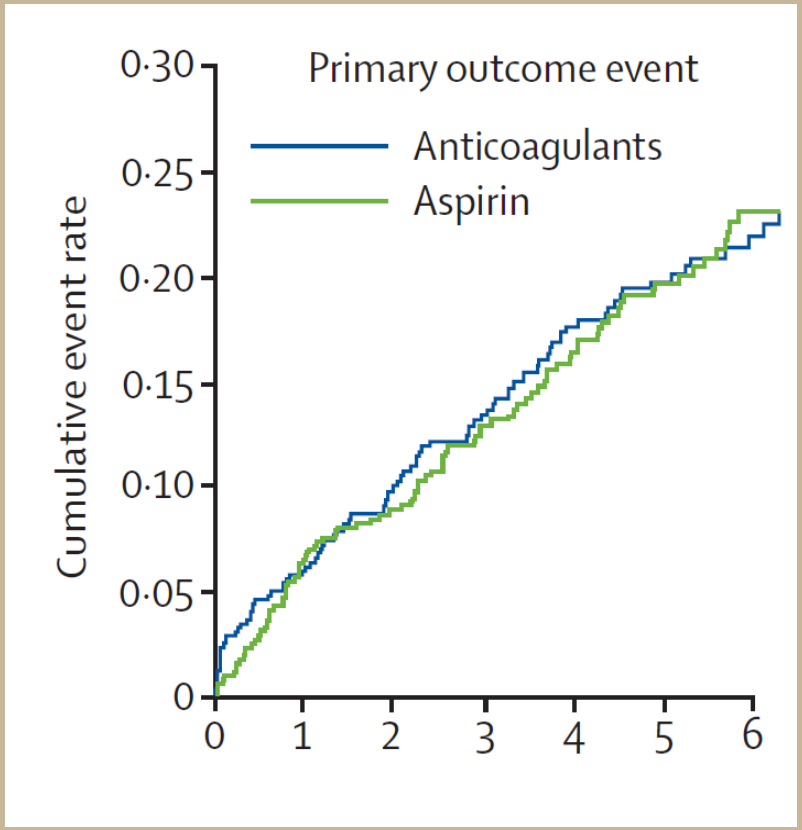
Glotzer et al. Heart Rhythm 2015;12:234–241

	AF as a Risk Marker	AF as a Direct Cause
Concept	 • AF is a stroke risk marker that is epidemiologically associated with stroke, not necessarily always causative	AF directly leads to LAA thrombus formation and risk of cardioembolic stroke 
Implications for the definition of a critical AF threshold	• Need to determine sufficient burden/duration of AF that associates with risk	• How much AF is needed to promote LAA thrombus formation? • Need to determine temporal relationships, burden, etc.
Therapeutic implications	• AF burden less important • Treat AF along with other risk factors • Minimal role for rhythm control as a stroke reduction strategy • Anticoagulation should not be stopped post ablation	• Role for "pill in the pocket" anticoagulation? • Role for rhythm control as a strategy for stroke reduction? • Role for continuous monitoring/tracking of PAF burden?

Circulation. 2019;140:e944–e963.

Warfarin Not Effective After Stroke Without AF





99 deaths (11 bleeds)
45 major bleed

98 deaths (4 bleeds)
18 major bleed

ESPRIT study group. *Lancet Neurol.* 6:115-124 (2007)

INNOVATION

NAVIGATE ESUS Study Stopped Early Due to Comparable Efficacy in Treatment Arms

Phase III study evaluated rivaroxaban versus aspirin in patients with embolic stroke of undetermined source with no atrial fibrillation

Study unlikely to show benefit of rivaroxaban versus aspirin if it were to be completed

RARITAN, NJ (October 5, 2017) – Janssen Research & Development, LLC and its development partner Bayer today announced the Phase III NAVIGATE ESUS study, evaluating the efficacy and safety of XARELTO® (rivaroxaban) for the secondary prevention of stroke and systemic embolism in patients with a recent embolic stroke of undetermined source (ESUS), is stopping early for futility. This decision is based on the recommendation of the study's Independent Data Monitoring Committee (IDMC) as the trial showed comparable efficacy between rivaroxaban and the standard of care, aspirin, and little chance of rivaroxaban showing an overall benefit versus aspirin if the study were to be completed. While bleeding rates were very low overall and within the expected range, an increase in bleeding was observed in the rivaroxaban arm compared to aspirin.

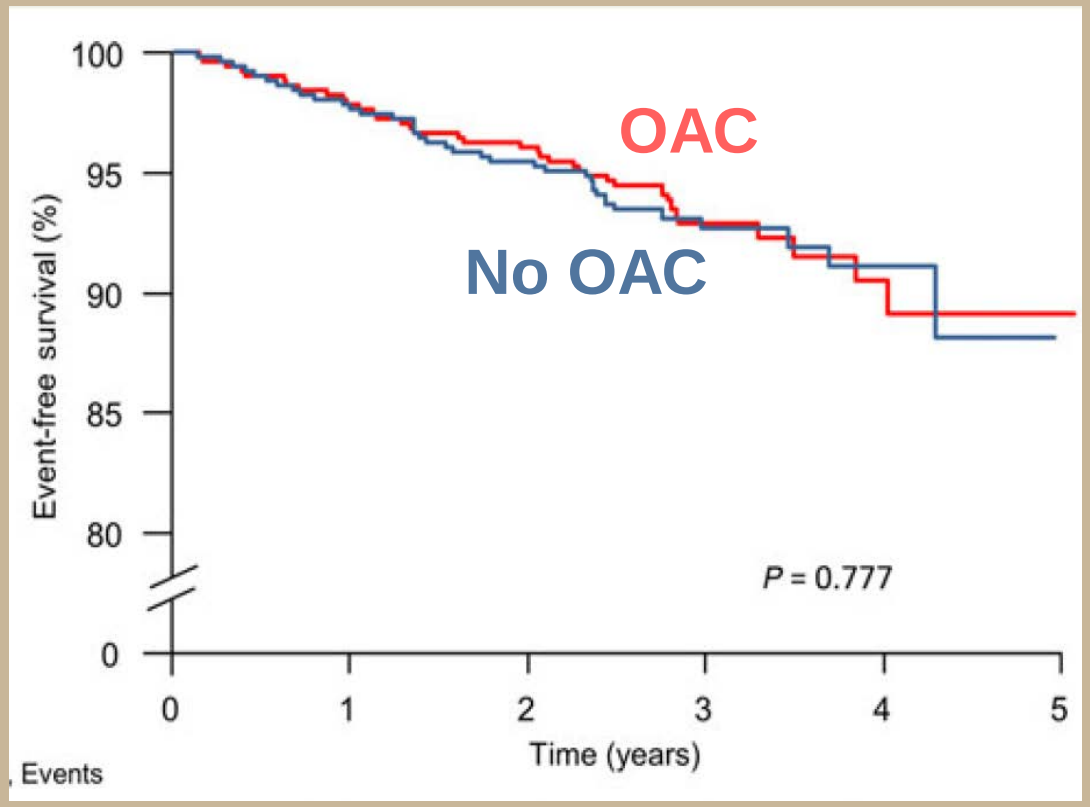
ESUS refers to patients with embolic stroke of unknown origin in whom common causes such as atrial fibrillation and carotid artery stenosis have been excluded. It is estimated to affect approximately 500,000 people in the United States annually.

Subsequent publication: N Engl J Med 2018; 378:2191-22

IMPACT:

Tailored Anticoagulation vs. Usual Care in Patients With AHRE

2718 CIED patients with AHRE, median CHA_2DSVA_2SC score 4, randomized to no anticoagulation (usual care) or anticoagulation initiated at times of AHRE and continued for 30 / 90 days (depending on CHA_2DSVA_2SC)



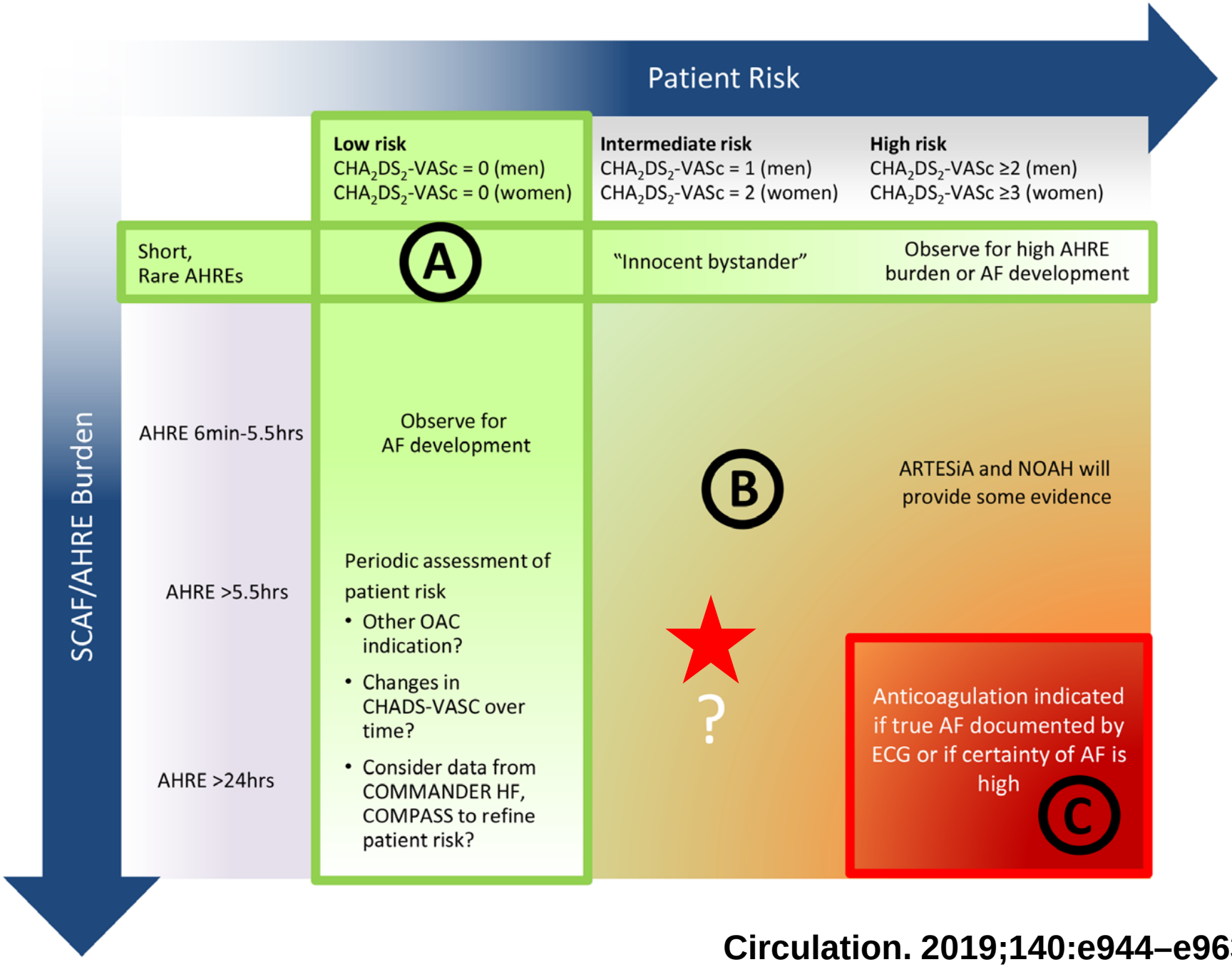
	OAC	No OAC
Stroke	0.7%	1.3%
Bleed	1.6%	1.2%
Death	5.4%	5.1%

Martin DT et al. *Eur Heart J* 36:1660-8.(2015)

63 yo man with hypertension, sinus node dysfunction and multiple episodes of asymptomatic AF recorded by PPM: CHA2DS2-VASc = 1

Episodes

Date / Time	Type	Peak A / V Rate (bpm)	Duration (D:H:M:S)
Jan 14, 2020 5:59 am	AMS Entry	640 / 167	0:02:08:42
Jan 14, 2020 12:28 am	AMS Entry	640 / 137	0:05:31:02
Jan 12, 2020 7:35 am	AMS Entry	199 / 61	0:00:00:06
Jan 4, 2020 11:52 am	AMS Entry	301 / 122	0:00:01:10
Jan 4, 2020 11:51 am	AMS Entry	295 / 110	0:00:00:18
Jan 4, 2020 11:47 am	AMS Entry	301 / 124	0:00:03:48
Jan 4, 2020 11:45 am	AMS Entry	290 / 123	0:00:01:28
Jan 4, 2020 11:45 am	AMS Entry	341 / 121	0:00:00:10
Jan 4, 2020 11:44 am	AMS Entry	233 / 85	0:00:00:06
Jan 4, 2020 11:44 am	AMS Entry	265 / 122	0:00:00:14
Jan 4, 2020 11:44 am	AMS Entry	199 / 74	0:00:00:04
Jan 4, 2020 11:43 am	AMS Entry	279 / 121	0:00:00:52
Jan 4, 2020 11:35 am	AMS Entry	313 / 122	0:00:01:52
Jan 4, 2020 11:34 am	AMS Entry	279 / 122	0:00:01:40



Circulation. 2019;140:e944–e963

ARTESiA Study Design

ARTESiA

Clinicaltrials.gov
NCT01938248

Patients with:
- **SCAF (at least 1 episode ≥ 6 min but none > 24 hrs)**
- **CHA_2DS_2-VASc score ≥ 3**
- **No clinical AF, contraindication or requirement for anticoagulation**

CONSENT and RANDOMIZE

Active aspirin
81mg qd
+
Placebo apixaban bid

Active apixaban
5mg or 2.5mg bid
+
Placebo aspirin qd

<u>Primary Efficacy Outcomes:</u>
Stroke (including TIA with imaging)
Systemic Embolism

<u>Primary Safety Outcomes:</u>
Major Bleeding

Flow chart of NOAH – AFNET 6

Inclusion criteria

Age > 65 and one additional CHA_2DS_2VASc factor

and

documented atrial high rate episode > 6 mins

Exclusion criteria

conventionally diagnosed AF indication for oral anticoagulation contraindication for NOAC therapy

R

Oral anticoagulation therapy (NOAC) with Edoxaban

ASA or placebo

Primary outcome:

stroke, systemic embolism, or cardiovascular death

Clinicaltrials.gov NCT02618577

Conclusions

- AF burden is relevant to stroke risk.
  - Threshold for risk? Continuum of risk?
- SCAF/AHREs are VERY common and increase risk (< clinical AF)
- Reasons for weak temporal relationship between AF episodes and stroke events?
- Differential impact of AF burden and various CHA2DS2-VASc scores?
- ARTESiA and NOAH may provide some answers.

Circulation

AHA SCIENTIFIC STATEMENT

Subclinical and Device-Detected Atrial Fibrillation: Pondering the Knowledge Gap

A Scientific Statement From the American Heart Association

Circulation. 2019;140:e944–e963

Thank you